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Lady Davis Institute
Research Newsletter

McGill

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CIHR operating grants awarded

In the latest Canadian Institutes for Health Research (CIHR) funding competition, the following LDI investigators were awarded support for their research:

Dr, Marc Fabian (cancer) was awarded $141,000 per year for five years for "Action of the CCR4-NOT complex in mammalian gene silencing networks;"

Dr. Anne Gatignol (HIV/AIDS) was awarded $100,000 bridge funding for "Virus-cell interactions in the regulation of HIV translation;"

Dr. Christina Greenaway (Epidemiology) gets $79,000 per year for three-and-a-half years for "Universal Childhood Varicella Vaccination Program: Will it protect or harm the immigrant population?"

Dr. Celia Greenwood (Cancer) was awarded $101,000 per year over four years for "Analysis of DNA methylation data;"

Nathalie Johnson (Cancer) will be funded $150,000 per year for the next three years for "Overcoming therapeutic resistance in lymphoma;"

Dr. Stephanie Lehoux (Hemovascular) was awarded $127,000 per year for five years for "Potential roles of Semaphorin 3A in atherosclerosis;"

Dr. Rongtuan Lin (Cancer) will be funded $166,000 per year over five years for "Manipulating the RIG-I signaling pathway to inhibit influenza virus infection."

CCS Innovation Grants

To support unique and creative research, the Canadian Cancer Society has awarded Innovation Grants to:

Dr. Mark Basik, $200,000 over two years to investigate the role of carcinoma-associated fibroblasts in drug resistance in breast cancer;

Dr. William Foulkes, $200,000 over two years for "DICER1 and pituitary blastoma: Keys to understanding pituitary development and tumorigenesis;"

Dr. Josie Ursini-Siegel, $200,000 over three years to study molecular mechanisms governing breast cancer immunosuppression.

Movember Discovery Grants

Three LDI scientists were awarded Prostate Cancer Canada Movember Discovery Grants. Each is worth $200,000 over two years to support new and important directions in prostate cancer research:

Dr. Rongtuan Lin is exploring the use of an oncolytic virus (OV) in combination with a small molecule to develop a novel treatment. Resistant prostate cancer cells respond more easily to the therapeutic effects of the OVs when combined with small molecule drugs.

Dr. Mark Trifiro's lab has identified new proteins that interact with androgen receptors, a hormone that has been identified with the growth and progression of prostate cancer. His project, led by Dr. Miltiadis Paliouras, aims to identify the androgen receptor signaling pathways that lead normal cells to mutate into cancer.

Dr. Jian Hui Wu is working on a new chemical inhibitor of the ETS oncoprotein, which is over-expressed in half of all prostate cancer patients. Dr. Wu has discovered a novel small molecule that inhibits the function of this oncoprotein and could, therefore, lead to the emergence of a new class of anti-prostate cancer drugs.

2013 CliPP Recipients

The 2013 Clinical Research Pilot Project (CliPP) grants have been announced. CliPP provides operating funds so that LDI principal investigators can launch pilot clinical research projects to obtain preliminary data that will enhance their ability to attract external peer-reviewed funding for clinical research. Recipients are selected following a competitive internal review. Out of nine submissions, grants were awarded to:

Dr. Gerasimos J. Zaharatos for "Telomere length analysis of HIV antigen-specific memory B-cells;" and

Dr. Kostas Pantopoulos for "Iron overload as cofactor for liver disease in HIV Infection: Exploring prevalence and the pathogenic role of hepcidin and proinflammatory cytokines."

The next CliPP competition will be announced in early 2014.

An emerging story in pediatric cancer

Dr. William Foulkes has been awarded a major grant from Alex's Lemonade Stand Foundation for Childhood Cancer to pursue his innovative research into the link between the gene DICER1 and a variety of pediatric cancers. The grant is for $250,000 over two years.

"DICER1 Syndrome, as it's called, is interesting because, though rare, DICER1 mutations are present in an unusual spectrum of pediatric cancers, including a form of pediatric lung tumor known as pleuro-pulmonary blastoma (PPB) and an ovarian cancer that strikes at young adults," Dr. Foulkes said. "Remarkably, it only seems to have a tumor-producing effect until age 30 or so, at which point it mysteriously shuts off. We want to understand what regulatory mechanisms are responsible for turning it on and off."

DICER1 regulates the expression of other genes by controlling microRNA. Though its effects are not fully understood, it has been shown that embryonic stem cells, the building blocks for life, die when it is knocked out.

"DICER1 is critical for development. Why does it cause these incredibly rare cancers? There's some kind of switch that has to be flipped on before the age of 10 or thereabouts for the mutation to have any effect, otherwise something else takes over," Dr. Foulkes speculates.

It is believed that, when functioning properly, DICER1 plays a role in tumor prevention. Only when affected by a particular mutation is it responsible to inciting tumor formation. Dr. Foulkes has successfully linked DICER1 mutations to a number of rare tumors – of the brain, kidney, cervix and pituitary gland – that previously were not known to be related to DICER1.

His lab has also uncovered a second DICER1 mutation that is not inherited, which initiates the development of PPB. The finding was published in *Pediatric Blood & Cancer*. Another recent study from his lab showed that these second mutations can also occur in Wilms Tumor, the most common kidney tumor in childhood.

Leanne DeKock, a Master's student under Dr. Foulkes' supervision, was awarded an LDI TD Studentship Award earlier this year to study pituitary blastoma, a newly identified and very rare form of brain tumor that occurs in young children, and has been linked to DICER1.

What is exciting about this research is the promise to reveal a causal pathway to explain the genetics underlying a diverse group of pediatric cancers.

Pioneering biobanking promises more in-depth genetic profiling of cancers

New clinical protocols need to be developed for taking biopsies of malignant tumors at different stages of their growth in order to build next-generation biobanks. This will enable researchers to accurately study and compare how the genetic composition of cancer cells evolves over time and leads to resistance to drug therapies. It will assist physicians in prescribing a course of treatment that targets the molecular foundation of a patient's cancer and in adjusting those treatments according to changes in the make-up of the disease.

"The distressing reality is that metastatic solid tumours are almost never curable because they become progressively resistant to serial drug therapies; there seem to be no signs on the clinical horizon that might provide a way to overcome this issue," wrote **Dr. Mark Basik** in the latest issue of *Nature Reviews Clinical Oncology*. "Clearly, now is the time to focus attention on the molecular analysis of recurrent, metastatic, and drug resistant tumours."

The advent of personalized medicine is a reflection of the growing body of evidence that cancer cells mutate in various and unpredictable ways in their struggle to survive in the face of therapies deployed against them. As this occurs, drugs gradually lose their effectiveness and patients eventually succumb. Great advances in analytic technology, along with accelerated drug development and a growing understanding of tumour heterogeneity, have resulted in next-generation biobanking, which calls for serial biopsies to monitor changes in metastatic cancer over time.

With the realization that each cancer has the potential to run a distinct course, there is a growing demand for multi-centre studies. They provide the capacity for comparative analysis of larger numbers of tumour samples, thereby increasing the data available to identify therapies most likely to be effective for each patient. In a paper published in the latest edition of *Modern Pathology*, **Dr. Gerald Batist** and colleagues propose a standardized protocol for performing needle core biopsy, in this case for liver cancer.

"It is a complex process, requiring detailed work-flow across a variety of disciplines, to ensure the quality and usability of patient specimens," acknowledged Dr. Batist. He is, however, clear that next-generation biospecimens are key to the future of cancer research and treatment over the coming decade.

High mortality rates for VTE despite preventive strategies

The risk of venous thromboembolism (VTE), which includes blood clots deep in the leg veins (deep vein thrombosis) or in the lungs (pulmonary embolism), is high, particularly among the elderly and cancer patients, according to the first study to use public health data to explore the condition's incidence and mortality in a Canadian population. The research, led by **Dr. Vicky Tagalakis** and based on public health databases in Quebec from 2000 to 2009, was published in the *American Journal of Medicine*.

"Even though we have made great strides in promoting the prevention of VTEs, we fully expected to uncover that the incidence may still be high because of our rapidly aging population," according to Dr. Tagalakis. The study found a rate of roughly 1.2 new VTE cases per 1,000 person-years which is similar to rates found by earlier studies. Moreover, VTEs are eight times more probable in patients over the age of 80 than in patients who are 50 or younger. The 30-day fatality rate following a VTE was more than 10%, while the fatality rate after one year was 23%.

Two-thirds of VTE cases are provoked, with the most common triggering factors including cancer, recent surgery, and recent hospitalization (62%). Consequently, a variety of preventive strategies are employed in hospital settings, such as administering pre-emptive anti-clotting medication immediately following surgery. The remaining one-third of VTE cases are unprovoked and, thus, unexplained.

In those individuals where the VTE has been provoked, it is an isolated event, the risk for which dissipates with the resolution of the accompanying illness or recovery from surgery. However, those who suffer an unprovoked VTE have up to a 30% risk of having more blood clots in the future, and in these individuals VTE is considered to be a chronic cardiovascul ar condition.

Cancer patients who develop VTE have a poorer prognosis than those who don't. The exact reasons are unclear, but it could be because VTE is an indicator that a more aggressive cancer is at work.

"We are conducting research to identify which cancer patients are more susceptible to VTE, as well as to better understand why the disease is more frequent in older than younger populations. In doing so, we will be better positioned to develop preventive strategies that target at-risk individuals." Dr. Tagalakis said.

Link between androgen deprivation therapy and acute kidney injury

An epidemiological study led by **Dr. Samy Suissa** revealed that androgen deprivation therapy (ADT), which has been the mainstay treatment for patients with advanced prostate cancer, is associated with a significantly increased risk of acute kidney injury (AKI). The results were published in *JAMA*.

"ADT is increasingly being used in patients with less severe forms of the cancer, such as in patients with biochemical relapse who have no evidence of metastatic disease. Although ADT has been shown to have beneficial effects on prostate cancer progression . . . the testosterone suppression associated with this therapy may lead to a hypogonadal condition that can have detrimental effects on renal function, thus raising the hypothesis that ADT-induced hypogonadism could potentially lead to acute kidney injury," according to the study. The mortality rate for patients with AKI is around 50 percent.

The data, drawn from the UK Clinical Practice Research Datalink, included more than 10,000 men newly diagnosed with non-metastatic prostate cancer between 1997 and 2008, who were followed up until December 2009. During follow-up, 232 cases with a first-ever AKI admission were identified. All cases were matched with at least one control. The researchers found that current use of ADT, as compared with never using ADT, was significantly associated with a 2.5 times increased chance of developing AKI.

"This association was mainly driven by a combined androgen blockade consisting of gonadotropin-releasing hormone agonists with oral antiandrogens, estrogens, other combination therapies, and gonadotropin-releasing hormone agonists," the study found.

"To our knowledge, this is the first population-based study to investigate the association between the use of ADT and the risk of AKI in men with prostate cancer. In this study, the use of ADT was associated with an increased risk of AKI, with variations observed with certain types of ADTs. This association remained continuously elevated, with the highest odds ratio observed in the first year of treatment. Overall, these results remained consistent after conducting several sensitivity analyses," the authors write. "These findings require replication in other carefully designed studies as well as further investigation of their clinical importance."

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Vitamin C therapy may reduce distress in hospitalized patients

When patients on medical and surgical units at the Jewish General Hospital were administered vitamin C, their measured levels of mood disturbance and psychological distress rapidly and markedly decreased, according to the results of a randomized clinical trial led by **Dr. L. John Hoffer.**

While previous studies have documented abnormally low vitamin C and D levels in more than half of all acutely hospitalized patients, the medical importance of these abnormalities has been unknown. Consequently, very few patients are currently prescribed a vitamin supplement while in hospital.

Since vitamin C and D deficiency have both been linked to mood and psychological disturbances, Dr. Hoffer initiated a double-blind randomized controlled trial to test the psychological effects of vitamin C or D replacement in acutely hospitalized patients.

Patients whose low vitamin C levels were corrected experienced a rapid and pronounced lessening of psychological distress and mood disturbance (by a measure of approximately 50%), whereas patients treated with vitamin D experienced no significant change in mood or distress. Regarding this latter conclusion, it turned out that the dose of vitamin D administered (5000 IU per day) was not enough to normalize the patients' vitamin D levels during the short duration of the study.

According to Dr. Hoffer, acutely ill hospitalized patients have abnormally low vitamin C levels because of a combination of poor nutrition and metabolic stress.

"Our study was relatively small – only 52 participants – but the results are potentially extremely pertinent to good in-hospital care," said Dr. Hoffer. "We have shown that it is easy to correct deficient vitamin C status with simple vitamin C supplementation. Correction of vitamin C deficiency can dramatically improve patients' ability to tolerate the serious psychological stresses associated with an acute hospital admission. There could be other physiological benefits as well.

This study was published in the *American Journal of Clinical Nutrition*.

A pathway to hypoxia

A study by **Dr. Kostas Pantopoulos**, published in *Blood*, has demonstrated *in vivo* that iron regulatory protein 1 (IRP1) is the principal regulator of hypoxia inducible factor 2*a* (HIF2*a*) mRNA translation. HIF2α is a subunit of HIF, which activates more than 100 target genes that control adaptation to hypoxia, or oxygen starvation within cells.

Clinically, hypoxia occurs during a heart attack or stroke. As well, hypoxia is a hallmark of several tumors. While up-regulation of HIF is beneficial during ischemia, it may be detrimental in cancer because it promotes the survival of the malignancy. Consequently, the HIF pathway is a drug target to inhibit tumor growth.

It was recently demonstrated in *in vitro* studies that HIF2*a* expression is regulated by iron and may play a role in iron metabolism, which is a focus of Dr. Pantopoulos' research. The next logical step was for him to test this hypothesis in a mouse model.

"We began initiating experiments to discover the *in vivo* relevance of this finding by using mice, which lack IRP1 expression. These animals were previously reported to lack any discernible pathology," he explained. "We demonstrated that juvenile IRP1 knockout mice develop polycythemia, a hematological disease caused by excessive levels of red blood cells that affects the viscosity of the blood. This is caused by translational activation of HIF2α mRNA. Accumulation of HIF2*a* induces the expression of erythropoeitin, a hormone which, in turn, promotes the differentiation of red blood cells that are responsible for carrying oxygen to tissues."

Dr. Pantopoulos will be pursuing early data that defects in the IRP1-HIF2*a* pathway may be responsible for some defects in glucose metabolism, as well as cancer. He has received a grant from the Canadian Institutes for Health Research (CIHR) to fund this research.

"IRP1 regulates erythropoiesis and systemic iron homeostasis by controlling HIF2*a* mRNA translation" by Nicole Wilkinson and Kostas Pantopoulos appears in *Blood.*

SAVE THE DATE!
5th Annual LDI Scientific Retreat
Friday May 30, 2014
Holiday Inn—Midtown Montreal
Keynote Speaker: Dr. Morag Park,
Director, Goodman Cancer Centre,
McGill University